Chinese Journal of Natural Medicines

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Citation: Kaijie Yan, Sihe Gong, Yanni Li, Zhonghong Shi, Yimin Bao, Jing Leng, Ke Ning, The signaling pathways of atherosclerosis regulated by Taohong Siwu Decoction, Chinese Journal of Natural Medicines, 2026, 24(3), 279−288. doi: 10.1016/S1875−5364(26)61103−X.

View online: https://doi.org/10.1016/S1875−5364(26)61103−X

Chinese Journal of Natural Medicines 24 (2026) 279-288

Contents lists available at ScienceDirect

Chinese Journal of Natural Medicines

journal homepage: www.cjnmcpu.com/

Review

The signaling pathways of atherosclerosis regulated by Taohong Siwu Decoction

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ARTICLE INFO

Article history:
Received 4 March 2025
Revised 11 June 2025
Accepted 13 June 2025
Available online 20 March 2026

Keywords:
Atherosclerosis
Traditional Chinese medicine
Taohong Siwu Decoction
Signaling pathways

ABSTRACT

Taohong Siwu Decoction (THSWD), a traditional Chinese medicinal formulation, has been demonstrated to significantly modulate key signaling pathways implicated in atherosclerosis (AS). This review examines the complex mechanisms through which THSWD influences critical pathways, including nuclear factor kappa-B (NF-κB), phosphatidylinositol 3-kinase (PI3K)/serine-threonine kinase (AKT), Toll-like receptor 4 (TLR4), mitogen-activated protein kinase (MAPK), and mammalian target of rapamycin (mTOR), that play pivotal roles in AS pathogenesis. By synthesizing experimental evidence and existing literature, the review summarizes how THSWD and its bioactive constituents regulate these signaling cascades to ameliorate AS. Furthermore, it highlights the distinctive therapeutic advantages of traditional Chinese medicine (TCM) compounds in managing chronic diseases driven by multi-target and multifactorial mechanisms. Analyzing disease targets from the perspective of signaling pathways enhances the scientific validation of clinical efficacy for such formulations, thereby offering novel insights for future research.

1. Introduction

Atherosclerosis (AS) is considered one of the major causes of cardiovascular disease, primarily initiated by arterial endothelial cell damage, followed by a cascade of events including lipid accumulation, fibrous plaque formation, and plaque rupture. The inflammatory response is involved in nearly all stages of AS. During AS progression, endothelial dysfunction, lipid metabolism disorders, inflammation, and platelet activation are interrelated processes that collectively influence plaque development and destabilization. The vascular damage caused by AS can affect virtually all organs and has become a fundamental contributor to many common diseases in middle-aged and elderly individuals, posing a serious threat to human health and longevity. Taohong Siwu Decoction (THSWD), a classical formula for regulating menstruation, was first documented in the 'Golden Mirror of Medicine' compiled by Qian Wu, a renowned traditional Chinese medical practitioner during the Qing Dynasty. THSWD consists of Angelicae Sinensis Radix, Paeoniae Radix Alba, Chuanxiong Rhizoma, Rehmanniae Radix Preparata, Persicae Semen, and Carthami Flos, and exerts dual effects of promoting blood circulation to resolve stasis and nourishing and replenishing blood. Modern pharmacological studies indicate that THSWD possesses anti-inflammatory [1], anti-platelet [2], anti-aggregation [2], lipid-lowering [3], antioxidant [4], vascular endothelial protective [5], hemorheological-improving properties [6]. These actions directly target key pathological stages of AS, exerting a positive regulatory effect on its progression. Consequently, THSWD has been clinically applied in the treatment of AS, and numerous studies have demonstrated its efficacy [7–9], offering a safe and effective traditional Chinese medicine (TCM)-based approach for the prevention and management of AS.

A study [10] employed UPLC-Q-TOF-MS to qualitatively analyze and identify the components of THSWD, revealing that aromatic acids (e.g., ferulic acid, caffeic acid, coumaric acid, gallic acid), glycosides (e.g., paeoniflorin, albiflorin, rehmannioside, amygdalin), and phthalides (e.g., ligustilide) present in THSWD inhibit ADP-induced platelet aggregation and thrombin activity *in vitro*. These findings provide a scientific basis for THSWD's role in promoting blood circulation and resolving stasis. In TCM, Persicae Semen is believed to activate blood and dispel stasis. Experimental studies [11] have confirmed that Persicae Semen and its extracts reduce blood viscosity, enhance local blood flow, and improve hemorheological parameters. Its main active constituents include amygdalin and peach kernel oil. Carthami Flos promotes blood circulation, removes stasis, and relieves pain. A review [12] summarized recent findings on the chemical composition of Carthami Flos, identifying safflor yellow A, safflor yellow B, hydroxysafflor yellow A, quercetin, luteolin, baicalin, and kaempferol as primary components. Chuanxiong Rhizoma is recognized as a key herb with cardiovascular protective effects in clinical practice. Its principal bioactive compounds include ligustilide, senkyunolide, ferulic acid, and gallic acid [13]. Angelicae Sinensis Radix invigorates blood and nourishes blood. As a member of the Apiaceae family, it shares considerable chemical similarity with Chuanxiong Rhizoma [14]. Paeoniae Radix Alba is traditionally used to nourish blood and regulate menstruation. Its bioactive constituents [15] include paeoniflorin, gallic acid, and albiflorin, with paeoniflorin

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https://doi.org/10.1016/S1875-5364(26)61103-X

being the most abundant compound and specific to the genus *Paeonia*. Rehmanniae Radix Preparata tonifies blood and nourishes yin. Research [16] has identified its chemical components as rehmannioside, catalpol, acteoside, sitosterol, and stigmasterol (Table 1).

In this review, we summarize the signaling pathways through which THSWD primarily exerts its therapeutic effects on AS (Table 2), discuss the roles and mechanisms of these pathways in AS pathogenesis, and outline how THSWD and its bioactive constituents modulate these signaling cascades. This synthesis is based on extensive experimental evidence and existing research, aiming to support future investigations in this field.

2. Signaling pathways in AS regulated by THSWD

2.1. Nuclear factor kappa-B (NF-κB) signaling pathway

2.1.1. Overview of NF-κB signaling pathway

NF-κB is a family of inducible transcription factors involved in regulating diverse cellular processes such as proliferation, apoptosis, and inflammatory responses. It plays a critical role in innate and adaptive immunity by controlling the expression of cytokines and chemokines, and is widely recognized as a central regulator of inflammation.

The NF-κB family comprises five subunits: NF-κB1 p50, NF-κB2 p52, RelA (also known as p65), RelB, and c-Rel, which typically form hetero- or homodimers. These dimers are sequestered in the cytoplasm by inhibitory proteins known as inhibitor of NF-κB (IκB). Upon stimulation, they dissociate from IκB and translocate to the nucleus to regulate target gene transcription [17]. Additionally, the precursor proteins p105 (NF-κB1) and p100 (NF-κB2) exhibit IκB-like functions due to their C-terminal structural similarity to IκB [18].

This pathway operates *via* two distinct branches: the canonical and non-canonical pathways. The canonical pathway is activated by various receptors, including Toll-like receptors (TLRs) [19], cytokine receptors, pattern recognition receptors (PRRs), tumor necrosis factor receptors (TNFRs), T cell receptors (TCRs), and B cell receptors (BCRs) [20]. Activation leads to transforming growth factor β (TGF-β)-activated kinase 1 (TAK1)-mediated phosphorylation of IκB kinase (IKK), resulting in IκBα ubiquitination and degradation. This releases p50/RelA and p50/c-Rel dimers, allowing nuclear translocation and initiation of gene transcription [17]. In contrast, the non-canonical pathway depends on p100 processing, primarily triggered by ligands of specific TNFR superfamily members such as LTβR, BAFF-R, and cluster of differentiation 40 (CD40). This process involves NF-κB-inducing kinase (NIK)-mediated phosphorylation of p100, leading to its partial proteolysis into p52 and subsequent nuclear translocation of p52/RelB dimers [18].

2.1.2. Role of NF-κB in AS

Studies [21] have shown that the NF-κB signaling pathway is activated in human AS, with elevated DNA binding activity of NF-κB observed in nuclei within atherosclerotic plaques. This activity predominantly involves p50, RelA, and c-Rel, subunits of the canonical pathway, and lacks p52 and RelB, indicating that the canonical NF-κB pathway primarily mediates AS development.

This pathway contributes to plaque formation by upregulating pro-inflammatory mediators such as tissue factor (TF) and

Table 1 The effects of active ingredients from THSWD on signaling pathways of AS.

Active ingredient	Herb	Related signaling pathway	Mechanism	Outcome	Refs.
Amygdalin	Persicae Semen	NF-κB	NF-κB p65↓	Anti-inflammation	28
Quercetin	Persicae Semen, Carthami Flos	NF-κB	NF-κB p65↓, TNF-α↓	Anti-inflammation	29
		PI3K/AKT	PI3K↑, AKT↑	Inhibition of apoptosis	49
		TLRs	TLR4↓	Reduce cellular calcification	65
		MAPK	p38↓	Inhibition of macrophage senescence in plaques	79
		mTOR	mTOR↓	Activate autophagy	97
Luteolin	Carthami Flos	NF-κB	NF-κB p65↓	Anti-inflammation	30
Baicalin	Carthami Flos	MAPK	ERK1/2, JNK, p38↓	Anti-inflammation, Anti-oxidation	80
Ferulic acid	Chuanxiong Rhizoma, Angelicae Sinensis Radix	NF-κB	NF-κB p65↓	Anti-inflammation	31
		PI3K/AKT	PI3K↑, AKT↑	Inhibition of apoptosis	48
		TLRs	TLR4↓	Anti-inflammation	63
Senkyunolide A	Chuanxiong Rhizoma	NF-κB	NF-κB p65↓	Anti-inflammation	32
Ligustilide	Chuanxiong Rhizoma, Angelicae Sinensis Radix	MAPK	ERK, JNK, p38↓	Inhibition of cell proliferation	81
Paeoniflorin	Paeoniae Radix Alba	NF-κB	NF-κB p65↓	Anti-inflammation	33
		TLRs	TLR4↓, MyD88↓	Anti-inflammation	64
		MAPK	p38↓	Anti-inflammation	83
Kaempferol	Carthami Flos, Paeoniae Radix Alba	PI3K/AKT	PI3K/AKT/mTOR↓	Activate autophagy	50
		TLRs	TLR2 6↓, miR-5a-4p↑	Inhibition of apoptosis	66
Gallic acid	Chuanxiong Rhizoma,Paeoniae Radix Alba	MAPK	p38↓	Anti-inflammation	82
Paeonol	Paeoniae Radix Alba	mTOR	AMPK↑, mTOR↓	Activate autophagy, Inhibition of vascular smooth muscle cell proliferation	98
Catalpol	Rehmanniae Radix Preparata	NF-κB	NF-κB p65↓	Anti-inflammation	34–35
Acteoside	Rehmanniae Radix Preparata	NF-κB	NF-κB p65↓	Anti-inflammation	34–35

matrix metalloproteinases (MMPs). NF-κB activation also enhances the expression [19] of cytokines (tumor necrosis factor α (TNF-α), interleukin-1β (IL-1β), IL-6), chemokines (monocyte chemoattractant protein-1 (MCP-1)), and adhesion molecules (intercellular adhesion molecule-1 (ICAM-1) and vascular adhesion molecule-1 (VCAM-1)). These molecules promote leukocyte and monocyte recruitment to endothelial cells, where they differentiate into macrophages [22], internalize lipids to become foam cells, and initiate AS lesion formation.

However, evidence [23] suggests that suppressing NF-κB activation in macrophages may reduce anti-inflammatory IL-10 production and increase cell death, potentially exacerbating AS progression.

2.1.3. Regulation of NF-κB by THSWD

2.1.3.1 THSWD-mediated regulation of NF-κB signaling pathway

A recent study [24] demonstrated that in type 2 diabetic rats, THSWD treatment significantly suppressed NF-κB p65 expression, reduced TNF-α protein and messenger ribonucleic acid (mRNA) levels in myocardial tissue, and lowered serum concentrations of IL-1β and IL-6, thereby attenuating inflammatory factor expression. Another study [25] found that THSWD downregulates PTGS2 and NFKB1 target proteins in the NF-κB pathway, contributing to its anti-inflammatory effects. THSWD has also been shown to synergistically inhibit NF-κB when combined with other decoctions. For instance, Erchen Decoction and THSWD exhibit anti-atherosclerotic effects, possibly through inhibition of the Nox4/NF-κB/HIF-1α pathway [26]. Similarly, Baoyuan Decoction combined with THSWD reduces inflammation and vascular fibrosis [27]. Collectively, these findings demonstrate that THSWD mitigates AS progression by suppressing the activation of the NF-κB signaling pathway (Fig. 1).

2.1.3.2 Bioactive components of THSWD targeting NF-κB

Amygdalin, derived from Persicae Semen, inhibits the NF-κB/COX-2 pathway, thereby reducing inflammatory mediator expression, improving lipid profiles, and exerting anti-atherosclerotic effects [28]. Quercetin, an active constituent in bothCarthami Flos and Persicae Semen, suppresses nuclear translocation of the NF-κB p65 subunit and TNF-α release, blocking downstream gene expression and attenuating inflammation in AS [29]. Luteolin, a bioactive compound in Carthami Flos, inhibits IκBα degradation and subsequent p65 nuclear translocation, thus suppressing NF-κB signaling [30]. Ferulic acid, present in Angelicae Sinensis Radix and Chuanxiong Rhizoma, restrains NF-κB activation, modulates NF-κB-dependent expression of VCAM-1 and ICAM-1, and reduces inflammation [31]. Senkyunolide A from Chuanxiong Rhizoma significantly inhibits TNF-α expression, thereby interfering with NF-κB pathway activation [32]. Paeoniflorin, the major component of Paeoniae Radix Alba, prevents inflammatory responses by inhibiting oxidized (ox) LDL-induced phosphorylation of the NF-κB p65 subunit, thereby delaying AS progression [33]. Catalpol and acteoside, key constituents of Rehmanniae Radix Preparata, have been shown [34, 35] to inhibit p65 nuclear translocation in the NF-κB pathway, markedly reducing downstream inflammatory factor synthesis and alleviating the inflammatory response.

2.2. Phosphatidylinositol 3-kinase (PI3K)/serine-threonine kinase (AKT) signaling pathway

2.2.1. Overview of PI3K/AKT signaling pathway

The PI3K/AKT (also known as protein kinase B or PKB) pathway is a key intracellular signal transduction cascade regulating essential cellular functions such as protein synthesis, metabolism, angiogenesis, proliferation, apoptosis, and autophagy. It is intricately linked to inflammation, growth, and survival processes [36].

Central metabolites in this pathway include phosphatidylinositol-4,5-bisphosphate (PIP2) and phosphatidylinositol-3,4,5-trisphosphate (PIP3). Key regulatory genes are phosphatase and tensin homolog (PTEN) and phosphoinositide-dependent kinase-1 (PDK1). PI3K, a lipid kinase, is activated upon binding of growth factors, such as vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), and hepatocyte growth factor (HGF), to their respective receptors [36]. Activated PI3K catalyzes the conversion of PIP2 to PIP3 [37]. PTEN counteracts this process by dephosphorylating PIP3 at the 3' position, thereby limiting AKT activation and acting as a negative regulator [38].

PIP3 serves as a second messenger, recruiting PH domain-containing proteins like phosphoinositide-dependent protein kinase-1 (PDK1) and AKT to the plasma membrane. PDK1 then phosphorylates AKT, leading to partial activation [36]. Fully activated AKT regulates downstream effectors: it activates FOXO and GSK3 to control proliferation, and Tsc, Rheb, and mammalian target of rapamycin (mTOR) to regulate protein synthesis [39]. AKT also activates IKK, establishing crosstalk with the NF-κB pathway [40].

2.2.2. Role of PI3K/AKT in AS

Substantial evidence indicates that PI3Kγ, a key immune regulator [39], drives inflammatory responses in macrophages, neutrophils, and mast cells, thereby contributing to AS pathogenesis.

The PI3K/AKT pathway also influences macrophage polarization. Macrophages exist in two primary phenotypes: M1 and M2. Studies [41] show that M1 macrophages promote plaque development and instability, whereas M2 macrophages suppress inflammation [42] and are protective against AS progression. Deletion of the AKT1 isoform promotes M1 polarization and accelerates AS, while AKT2 deletion favors M2 differentiation and slows disease progression [43].

Macrophage apoptosis has dual roles in AS. In early lesions, apoptosis reduces foam cell accumulation and limits plaque expansion. However, in advanced plaques, macrophage apoptosis enlarges the necrotic core and increases the risk of rupture [44].

Table 2 Different mechanisms of signaling pathway regulation by THSWD.

Signaling pathway	Mechanism	Outcome	Refs.
NF-κB	NF-κB p65↓, TNF-α, IL-1β, IL-6↓	THSWD plays an anti-inflammatory role by regulating the NF-κB signaling pathway.	24
NF-κB	PTGS2, NFKB1↓		25
NF-κB	NF-κB p65↓, HIF-1α↓		26
PI3K/AKT	PI3K, AKT↑, eNOS↑, NO↑	THSWD plays an antioxidant and anti-inflammatory role by regulating the PI3K/AKT signaling pathway.	46, 47
TLRs	TLR4↓, NF-κB↓	THSWD plays an anti-inflammatory role by regulating the TLR signaling pathway.	60, 61, 62
MAPK	JNK, p38↓	THSWD inhibits pyroptosis by regulating the MAPK signaling pathway.	60, 78
mTOR	PI3K/AKT↓, mTOR↓	THSWD activates autophagy and reduces inflammatory response by regulating the mTOR signaling pathway.	96
mTOR	AMPK↑, mTOR↓		97

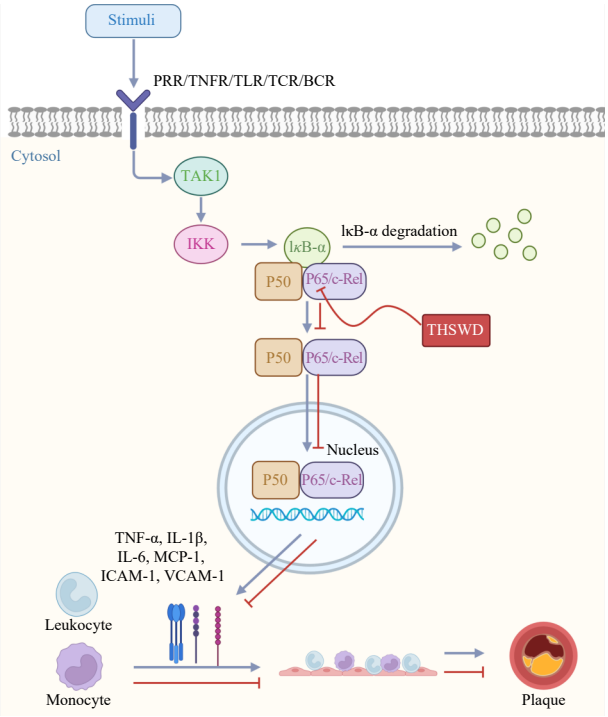

Fig. 1 Mechanism of THSWD regulating NF-κB signaling pathway in the treatment of AS. THSWD can inhibit the nuclear translocation of NF-κB p65 subunit, thus blocking the expression of related inflammatory factors, inhibiting leukocytes, monocytes, etc. from accumulating in the endothelial cells and differentiating into macrophages, which plays a role in inhibiting the formation of atherosclerotic plaques.

Since AKT signaling inhibits apoptosis [38], its activation may exert opposing effects depending on disease stage [44].

The activated AKT can catalyze the phosphorylation of eNOS at Ser-1177 and promote the release of NO [45]. NO can suppress the release and expression of inflammatory factors, the oxidation of LDL, the expression of cell adhesion protein, the migration and proliferation of vascular smooth muscle cells [6], which acts as an antioxidant and anti-inflammatory agent and inhibits the aggravation of AS. AKT signaling in macrophages functions as an inhibitor of apoptosis [38], which may affect different processes of AS differently.

Among the downstream molecules activated by this signaling pathway, it is worth mentioning eNOS and mTOR (the specific effects of this pathway will be described in detail in the mTOR signaling pathway). Activated AKT can catalyze the phosphorylation of eNOS at Ser-1177 and promote the release of NO [45], which can inhibit the release and expression of inflammatory factors, LDL oxidation, the expression of cell adhesion molecules (CAMs) expression, and the migration and proliferation of vascular smooth muscle cells (VSMCs) [6], and play an antioxidant and anti-inflammatory role and inhibit the aggravation of AS.

Collectively, the role of the PI3K/AKT pathway in AS is complex and context-dependent, with no single mechanism clearly dominating its overall impact.

2.2.3. Regulation of PI3K/AKT by THSWD

2.2.3.1 THSWD-mediated regulation of PI3K/AKT signaling pathway

A study [46] using Erchen Decoction combined with THSWD to treat ox-LDL-induced endothelial injury found significantly increased expression of PI3K and eNOS proteins and enhanced AKT phosphorylation in the intervention group compared to controls, along with reduced apoptosis. When a PI3K inhibitor (LY294002) was introduced, these effects were reversed, confirming the involvement of the PI3K/AKT pathway. Another study [47] showed that THSWD activates eNOS and elevates serum NO levels *via* PI3K/AKT signaling, suggesting that THSWD's therapeutic effect in AS may largely depend on eNOS activation and NO release through this pathway (Fig. 2).

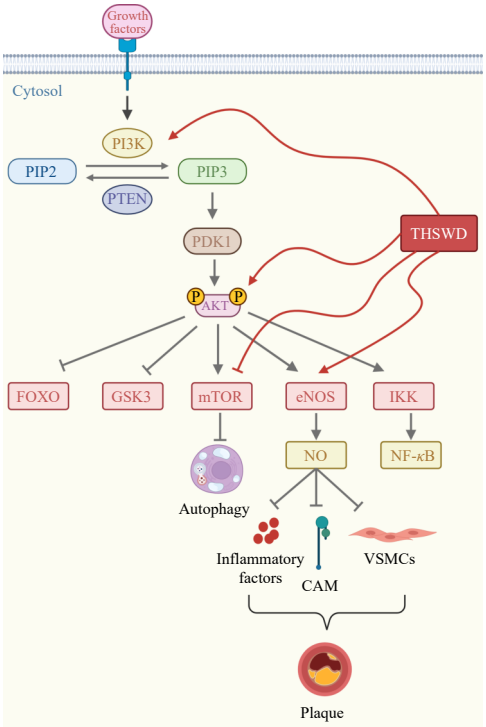

Fig. 2 Mechanism of THSWD regulating PI3K/AKT signaling pathway in the treatment of AS. In the downstream signaling, it inhibits the aggravation of AS by promoting the phosphorylation of eNOS and stimulating its release of NO, thereby inhibiting the release of inflammatory factors, the expression of CAM, and the migration and proliferation of VSMCs. THSWD can also enhance cellular autophagy by inhibiting the PI3K/AKT/mTOR signaling pathway, thereby stabilizing plaque.

2.2.3.2 Bioactive components of THSWD targeting PI3K/AKT

Ferulic acid has been shown [48] to enhance PI3K and AKT expression in cardiomyocytes, activating the pathway to prevent apoptosis and inhibit early plaque formation. Quercetin similarly enhances AKT activity and suppresses apoptosis [49]. Kaempferol, present in Paeoniae Radix Alba and Carthami Flos, has been found [50] to inhibit the PI3K/AKT/mTOR pathway, thereby enhancing autophagy and stabilizing atherosclerotic plaques.

2.3. Toll-like receptor (TLR) signaling pathway

2.3.1. Overview of the TLR signaling pathway

TLRs are a class of PRRs belonging to the type I transmembrane protein family. Their extracellular domains contain leucine-rich repeats (LRRs) and a Toll-interleukin-1 receptor (TIR) domain [51], enabling recognition of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) [52]. This recognition initiates downstream signaling cascades critical for both innate and adaptive immunity. TLR expression profoundly influences inflammatory responses and macrophage differentiation.

TLR signaling proceeds *via* two main pathways: myeloid differentiation primary response gene 88 (MyD88)-dependent and TRIF-dependent. Except for TLR3, all TLRs utilize the adaptor protein MyD88 *via* Toll-IL-1 receptor (TIR) domain containing adaptor protein (TIRAP) [52], leading to activation of NF-κB and mitogen-activated protein kinases (MAPKs), which stimulate pro-inflammatory cytokine production [53]. TLR3 and TLR4 can use the TRIF-dependent pathway: TLR3 directly recruits TRIF, while TLR4 requires TRAM AS a bridging adaptor [54]. TRIF activates

TRAF6 and TRAF3, which in turn induce NF-κB and MAPKs or activate IRF351 to promote interferon-β expression [51].

2.3.2. Role of TLRs in AS

Among TLRs, TLR4 is most closely associated with AS development. Research [55] indicates that increased lipid accumulation elevates TLR4 levels and enhances MyD88/TRIF signaling, accelerating AS progression and inflammation. Recent studies [56] show that ox-LDL binds to myeloid differentiation factor 2 (MD2) on macrophages, facilitating TLR4 activation and triggering downstream inflammatory cascades.

TLR4 mediates inflammation in multiple cell types. Monocyte accumulation at damaged sites is a hallmark of inflammation. Studies [57] report elevated TLR4 expression on circulating mononuclear cells in AS patients. TLR4 also mediates ox-LDL-induced macrophage activation, with Sub1 identified as a key regulator in macrophage-driven AS, likely through upstream regulation of IRF1 and promotion of M1 polarization, leading to plaque expansion [58]. Dendritic cell maturation is crucial in inflammatory cascades involving lipid accumulation, foam cell formation, and antigen presentation. Upregulation of TLR4 on dendritic cells activates endogenous responses and worsens AS [59].

2.3.3. Regulation of TLRs by THSWD

2.3.3.1 THSWD-mediated regulation of the TLR signaling pathway

A study [60] demonstrated that THSWD ameliorates ischemic stroke injury by inhibiting pyroptosis, and further revealed that THSWD suppresses TLR4 activation and downstream signals NF-κB and MAPK, thereby reducing inflammatory factor expression. In a rat model of rheumatoid arthritis [61], THSWD reduced joint swelling by downregulating the TLR4/NF-κB pathway. Another study [62] confirmed that THSWD intervention decreased mRNA and protein levels of TLR4, MyD88, and NF-κB in the model group. Thus, THSWD primarily attenuates inflammation by suppressing TLR4 and its downstream signaling components, slowing AS progression (Fig. 3).

2.3.3.2 Bioactive components of THSWD targeting TLRs

Network pharmacology analysis [63] indicated that ferulic acid's anti-AS mechanism is closely linked to the TLR4 pathway, with TLR4 being a core target. Paeoniflorin reduces expression of TLR4 and MyD88, and inhibits IκB and NF-κB p65 phosphorylation [64], thereby interrupting the inflammatory cascade. Quercetin attenuates ox-LDL-induced oxidative stress by dampening TLR4 signaling and reducing calcification [65]. Kaempferol not only modulates TLR4 but also alleviates ox-LDL-induced endothelial apoptosis by inhibiting the TLR2/6/NF-κB signaling pathway and upregulating miR-5a-4p, thereby exerting anti-atherosclerotic effects [66] to alleviate ox-LDL-induced endothelial apoptosis by suppressing the TLR2/6/NF-κB pathway and upregulating miR-5a-4p, thus inhibiting AS.

2.4. MAPK signaling pathway

2.4.1. Overview of the MAPK signaling pathway

MAPKs are AKTs activated by extracellular stimuli such as cytokines, neurotransmitters, and hormones. They regulate vital cellular processes, including growth, differentiation, development, and apoptosis. The MAPK cascade involves three sequential phosphorylation events: MAPK kinase kinase (MKKK), MAPK kinase (MKK), and finally MAPK [67], transmitting signals to the nucleus to initiate gene transcription. The best-characterized MAPK families are extracellular signal-regulated kinases 1/2 (ERK1/2), c-Jun *N*-terminal kinases/stress-activated protein kinases (JNK/SAPK), and p38 (with α, β, γ, δ isoforms).

In the ERK1/2 pathway, Ras-GTP binds Raf (the MKKK), which activates MEK1/2, subsequently phosphorylating ERK1/2 to execute its function [68]. The JNK/SAPK pathway is stimulated by ionizing radiation, heat shock, or inflammatory cytokines, with JNK activation mediated by mainly affected by MEK4 (MKK4) and MEK7 (MKK7) [67]; this upstream signaling overlaps with the p38 pathway. Similarly, the p38 pathway is activated by UV radiation, cytokines, or lipopolysaccharide. Signal transduction leads to phosphorylation of p38 primarily by MKK3 and MKK6, with MKK4 also contributing partially [69].

The ERK pathway is generally associated with cell proliferation and differentiation [70,71], whereas JNK and p38 pathways regulate not only proliferation but also inflammatory responses [72].

2.4.2. Role of MAPK in AS

The p38 MAPK pathway is particularly implicated in AS. It in-

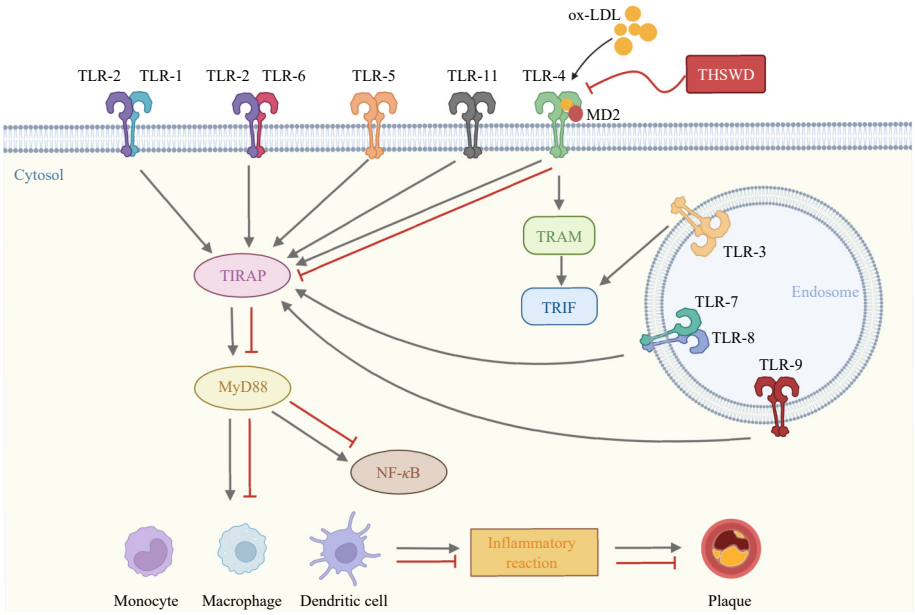

Fig. 3 Mechanism of THSWD regulating the TLR signaling pathway in the treatment of AS. THSWD is able to reduce the expression of TLR4 and MyD88, thus inhibiting the transduction of the TLR4/NF-κB signaling pathway. Moreover, THSWD can decrease the occurrence of inflammatory responses in different cells, such as monocytes, macrophages, and dendritic cells, by inhibiting the signaling of the MyD88-dependent pathway, which ultimately suppresses the formation of atherosclerotic plaques.

duces expression of inflammatory mediators such as VCAM-1 [73] and MCP-1 [74], promoting inflammatory cell infiltration and accelerating AS. Beyond inflammation, vascular calcification contributes to AS progression. Ceramide has been shown [75] to promote ox-LDL-induced VSMC calcification and apoptosis *via* p38 MAPK activation.

In addition to endothelial and VSMCs, the MAPK pathway is activated in macrophages. Ox-LDL induces p38-mediated macrophage proliferation, leading to foam cell formation and accelerating plaque development and rupture [76]. CD137 signaling has also been shown [77] to trigger mitochondrial fission *via* p38 MAPK, generating reactive oxygen species from dysfunctional mitochondria and promoting macrophage apoptosis, thereby expanding unstable plaques.

2.4.3. Regulation of MAPK by THSWD

2.4.3.1 THSWD-mediated regulation of MAPK signaling pathway

A study [60] reported that THSWD treatment significantly reduced JNK and p38 MAPK levels in rats with middle cerebral artery occlusion/reperfusion (MCAO/R), accompanied by decreased levels of inflammatory cytokines (TNF-α, IL-2, IL-6, TGF-β, IL-1β, IL-18). This suggests that THSWD may inhibit pyroptosis by suppressing the MAPK pathway. Another study [78], integrating network pharmacology, molecular docking, and experimental validation, confirmed that THSWD mitigates pyroptosis in ischemia-reperfusion injury by blocking MAPK signaling (Fig. 4).

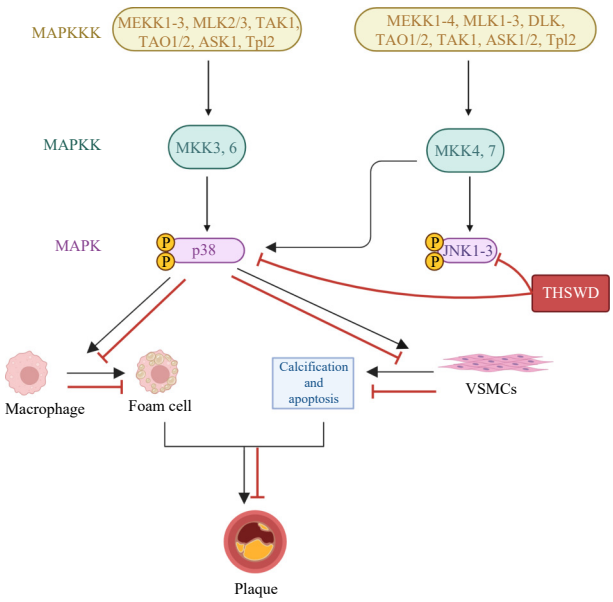

Fig. 4 Mechanism of THSWD regulating the MAPK signaling pathway in the treatment of AS. THSWD mainly inhibits the p38 MAPK signaling pathway, thus preventing macrophages from phagocytosis of lipids into foam cells as well as preventing VSMCs from undergoing calcification and apoptosis, and ultimately slowing down the production and rupture of atherosclerotic plaque. On the other hand, THSWD can also affect the JNK pathway, which may be related to the inhibition of inflammatory responses.

2.4.3.2 Bioactive components of THSWD targeting MAPK

Quercetin has been shown [79] to alleviate ox-LDL-induced senescence in plaque macrophages by inhibiting p38 MAPK/p16 phosphorylation, thereby slowing AS progression. Baicalin, a component of Carthami Flos, reduces activation of ERK1/2, JNK, and p38, indicating suppression of the MAPK pathway and conferring anti-inflammatory and antioxidant effects [80]. Ligustilide, present in Chuanxiong Rhizoma and Angelicae Sinensis Radix, dose-dependently suppresses ERK, JNK, and p38 activation, suggesting its role in modulating cell proliferation *via* MAPK inhibition [81]. Gallic acid, found in Chuanxiong Rhizoma and Paeoniae Radix Alba, attenuates inflammation by blocking p38 MAPK activation [82]. Paeoniflorin improves cardiac function in chronic heart failure by inhibiting the p38 MAPK pathway [83].

2.5. mTOR signaling pathway

2.5.1. Overview of the mTOR signaling pathway

mTOR is an atypical serine/threonine protein kinase belonging to the phosphatidylinositol kinase-related kinase (PIKK) family [84]. It integrates diverse extracellular signals to regulate cell proliferation, autophagy, and apoptosis, processes critically involved in AS plaque stability (Fig. 5).

mTOR forms two distinct complexes: mTOR complex 1 (mTORC1) and mTORC2. mTORC1 consists of five components [84]: mTOR (catalytic subunit), mLST8 (GβL), Raptor (substrate-recruiting protein *via* TOS motif [85]), PRAS40, and Deptor. The first three are core components; the latter two are inhibitory. mTORC2 contains six subunits [86]: mTOR, mLST8, Rictor, mSIN1, Protor1/2, and Deptor. The first four constitute the core. Notably, mLST8 is dispensable for mTORC1 activity but essential for mTORC2 function [87].

mTORC1 is regulated by growth factors, amino acids, oxygen, and energy status [88], and controls downstream processes such as protein, lipid, and nucleotide synthesis, as well as autophagy and catabolism. Key effectors include S6K1, 4EBP, sterol response element binding protein (SREBP), ULK1, and transcription factor EB (TFEB) [84]. mTORC2 is less well understood but is associated with cell survival, proliferation, and cytoskeletal remodeling. Its upstream signals originate mainly from insulin/PI3K signaling, and its downstream targets belong to the AGC kinase family. Notably, AKT and mTORC2 engage in a positive feedback loop: partial AKT activation promotes mTORC2 activation [89], which in turn fully activates AKT *via* phosphorylation.

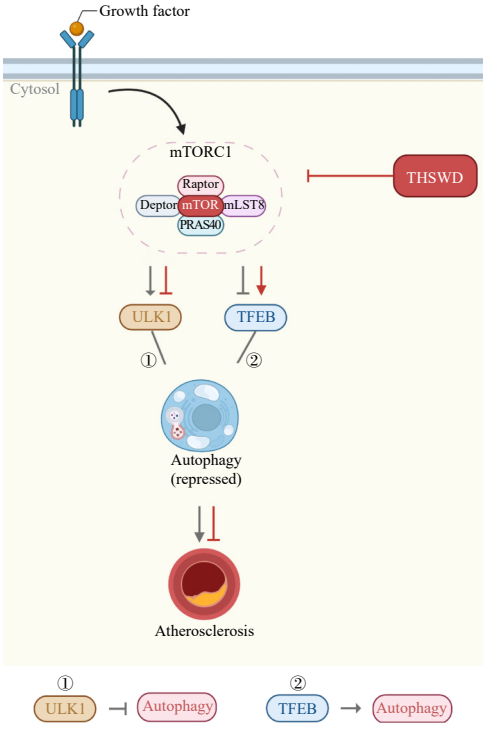

Fig. 5 Mechanism of THSWD regulating the mTOR signaling pathway in the treatment of AS. Cellular autophagy prevents endothelial cells from being damaged by exogenous lipid accumulation in the vascular wall and vascular stress, while ULK1 in the mTORC1 signaling pathway can inhibit autophagy, and TFEB can promote autophagy. THSWD can influence the mTORC1 signaling pathway to inhibit ULK1 phosphorylation, thus promoting the formation of autophagosomes. At the same time, THSWD can also stimulate the nuclear translocation of TFEB to promote cellular autophagy and ultimately inhibit the formation of AS.

2.5.2. Role of mTOR in AS

Autophagy protects against exogenous lipid accumulation and vascular stress in endothelial cells [90], thereby preventing AS. mTORC1 negatively regulates autophagy: adenosine 5'-monophosphate-activated protein kinase (AMPK)-mediated ULK1 activation is essential for autophagosome formation, but mTORC1 directly phosphorylates ULK1 to inhibit this process [91 92]. mTORC1 also suppresses autophagy [93] by blocking TFEB nuclear translocation. Foam cell formation, a hallmark of AS, is promoted by mTOR *via* inhibition of autophagy [92].

AS is a chronic inflammatory condition involving immune cells. In T cells, mTOR inhibition promotes a shift from effector to memory phenotype and suppresses $CD8^+$ T cell inflammation, contributing to plaque stabilization [94]. Additionally, mTOR modulates specific leukocyte subsets and inhibits immune cell proliferation, thereby dampening inflammation and slowing AS progression [95].

2.5.3. Regulation of mTOR by THSWD

2.5.3.1 THSWD-mediated regulation of the mTOR signaling pathway

A study [96] found that medium and high doses of THSWD significantly reduced mTOR mRNA and protein levels in rabbit tendon-bone interface tissues, indicating that THSWD suppresses mTOR expression, possibly *via* the PI3K/AKT/mTOR pathway (Fig. 6).

2.5.3.2 Bioactive components of THSWD targeting mTOR

Quercetin [97] suppresses mTOR expression, enhancing autophagy and reducing aortic root lipid accumulation in mice, thereby exerting protective effects against AS. Paeoniflorin activates AMPK and inhibits mTOR phosphorylation, promoting autophagy and suppressing VSMC proliferation [98].

3. Conclusion and prospect

In summary, the signaling pathways regulating AS described in this article have a close relationship with the treatment of THSWD, which can reduce the release of inflammatory factors, inhibit macrophage proliferation, reduce cellular calcification, and enhance cellular autophagy by promoting or inhibiting the above signaling pathways (Fig. 6). These pathways are likely to be the potential therapeutic targets of THSWD for AS. However, a large number of studies have found that there are numerous signaling pathways that can regulate the process of AS, such as the Wnt signaling pathway [99–100], the NLRP3 inflammasome [101–102], the RhoA/ROCK signaling pathway [103–104], the JAK/STAT signaling pathway [105], the Notch signaling pathway [106–107], and the VEGF signaling pathway [108–109]. However, few studies have correlated these pathways with the treatment of AS through THSWD. Several key questions remain to be addressed, including whether THSWD exerts therapeutic effects on atherosclerosis (AS) *via* the aforementioned pathways, and what specific molecular targets

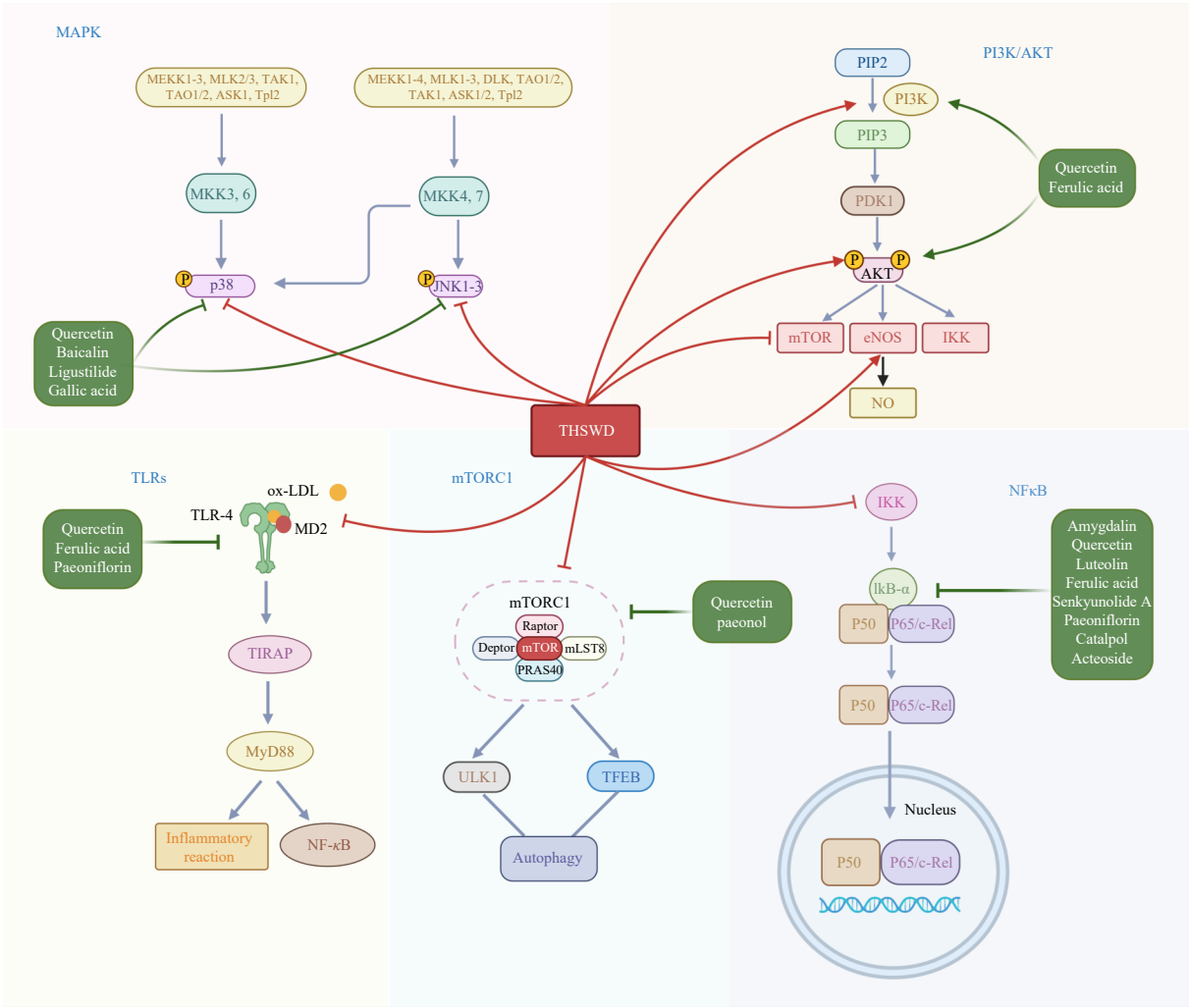

Fig. 6 The comprehensive connection between the signaling pathways of AS regulated by THSWD. THSWD can have different effects on NF-κB, PI3K/AKT, TLRs, MAPK, mTOR signaling pathways, and their downstream signaling molecules, and ultimately play a role in inhibiting the formation and development of atherosclerotic plaques. Among them, NF-κB, PI3K/AKT, TLR, and mTOR signaling pathways are interconnected and interact with each other, and are not a single independent signaling pathway.

and active components of THSWD are involved in these mechanisms. Further in-depth investigation is required to clarify these issues. Based on the potential cross-regulatory mechanisms between pathways that have not been thoroughly studied (e.g., Wnt, NLRP3, etc.) and those with well-elucidated mechanisms (e.g., NF-κB, TLR4 pathway, etc.), it provides the possibility of in-depth investigation and elaboration of the relationship between them and the treatment of AS with THSWD. For instance, in the Wnt signaling pathway, it has been pointed out [110] that Wnt signaling transduction is inextricably linked to the NF-κB and the TLR4 pathway during the regulation of inflammatory responses. Additionally, research [111] has also demonstrated that Wnts are able to activate p38 MAPK, and that the two interact with each other. In the NLRP3 inflammasome, study [112] concluded that MyD88- and TRIF-induced caspase-11 synthesis contributes to the activation of the NLRP3 inflammasome, suggesting a connection between the TLR4 signaling pathway and the NLRP3 inflammasome. In the RhoA/ROCK signaling pathway, Rho-kinase was shown [113] to inhibit the PI3K/AKT signaling pathway, thereby affecting downstream eNOS phosphorylation and NO release. It has been demonstrated [114] that the JAK/STAT signaling pathway exhibits crosstalk with the MAPK, PI3K/AKT, and NF-κB signaling pathways. Regarding the Notch signaling pathway, study [115] has revealed a positive feedback loop between Notch signaling and STAT3 after TLR activation, which involves several signaling pathways, including the TLR4, NF-κB, and JAK/STAT pathways. Additionally, research [108] has also demonstrated that VEGF activates STAT-3, NF-κB, and Akt pathways, creating crosstalk between the vascular and the inflammatory response.

A growing body of evidence indicates that TCM formulations offer significant advantages in managing complex, multifactorial chronic diseases. Unlike Western medicine's single-target approach, TCM treatment is guided by a holistic philosophy, enabling multi-target, multi-level, multi-pathway, and systemic regulation. The conventional drug development model in Western medicine typically follows a linear sequence: identification of disease-related targets, discovery of lead compounds, optimization of candidates, and subsequent pharmacodynamic, pharmacological, and clinical evaluation. While systematic, this approach may fail to capture the dynamic, staged, and multifactorial nature of chronic conditions such as AS [116]. In contrast, under the principles of "holistic regulation" and "treatment based on syndrome differentiation," TCM employs the classical formulation theory of "sovereign, minister, assistant, and courier" to rationally combine herbs. This enables TCM formulas to comprehensively regulate physiological functions, restore homeostasis, strengthen host defense, eliminate pathogenic factors [117], and simultaneously address both the symptoms and root causes of disease.

Nevertheless, it has been argued that the clinical application of TCM formulations lacks reproducibility and objective mechanistic validation when based solely on empirical observation and anecdotal efficacy. Therefore, elucidating the precise roles of TCM compounds through the lens of signaling pathways can provide robust scientific evidence for their therapeutic mechanisms. Furthermore, it is anticipated that future research will build upon this review to identify the primary bioactive components in THSWD. By screening and optimizing these constituents according to the principles of enhancing efficacy and minimizing toxicity, it may be possible to advance from crude herb compatibility to rational combinations of purified active ingredients. Such secondary development could yield formulations with superior pharmacodynamic profiles compared to the original prescription, while ensuring greater clarity and control over the key pharmacologically active substances.

The in-depth investigation of TCM formulations is not only essential for ensuring their safety and efficacy, promoting accurate understanding of herbal medicines, and objectively interpreting their disease-modifying mechanisms [118], but also holds broad implications for modern drug development and the global promotion of integrative preventive medicine. It is imperative to recognize that single-target interventions are often insufficient for preventing or treating increasingly prevalent complex chronic diseases. A paradigm shift is needed, one that emphasizes the value of comprehensive, systems-level approaches and fosters greater appreciation for the integrative effects of TCM formulations.

Funding

This work was supported by the National Natural Science Foundation of China (Nos. 82104430 and 82274133), the Shanghai Sailing Program (No. 21YF1447600), and the Future Plan for Traditional Chinese Medicine Development of Science and Technology of Shanghai Municipal Hospital of Traditional Chinese Medicine (No. WL-HBQN-2022002K).

Declaration of competing interest

These authors have no conflict of interest to declare.

Acknowledgements

We gratefully acknowledge the use of BioRender for the creation of the scientific illustrations in this study.

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